DOSAGE FORM DESIGN: A PHYSICOCHEMICAL APPROACH

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INTRODUCTION

Over the past several years, the fraction of new drug products that are new chemical entities has steadily decreased, reflecting the tremendous cost required to bring new chemical entities to the marketplace. Increased understanding of drug metabolic and toxicologic factors, such as the effect of the patient age on drug distribution, the genetic factors that may result in dramatic intersubject variability in metabolism, short-term versus long-term exposure toxicities, and the potential for teratogenic, mutagenic, and embryotoxic effects, has increased the scrutiny under which governmental agencies view the new chemical entity. This careful inspection is intended to minimize the possibility of toxic reaction(s) and to demonstrate the safety and efficacy of new drug products. The regulatory process has also resulted in significantly more costly and time-consuming testing prior to commercialization.

This increased emphasis on safety has placed an additional burden on those who are involved in the development of new drugs, while increasing financial pressures have led to the need for decreased development time. The investigation of approved drugs has resulted in enhanced patient safety and therapeutic efficacy by directing research efforts toward the more efficacious delivery of known pharmacologically active agents to the appropriate physiologic site. This trend has caused pharmaceutical researchers to seek the most suitable methods to deliver both new and existing compounds in the most pharmacologically appropriate manner. The methods may be designed to optimize bioavailability, minimize toxicity and side effects, and improve stability. The objective of this article is to present approaches that have been employed to improve bioavailability and/or minimize the toxicity and side effects of various drugs.

A rational approach to dosage form design requires a complete understanding of the physicochemical and biopharmaceutical properties of the drug substance. For example, the successful design of an efficacious oral dosage form requires an understanding of the pathways of physiologic disposition of the drug. Some of the physiologic factors associated with drug disposition are illustrated in Fig. 1 (1). On oral administration of an immediate release dosage form (the most common delivery system), the dosage form must disintegrate, the drug must dissolve in the gastrointestinal (GI) fluids, cross the GI mucosa, enter the mesenteric blood system, and pass through the liver prior to reaching the systemic circulation and the site of action. The drug may be metabolized by GI fluids, by enzymes in the gut wall, or by hepatic metabolism prior to reaching the systemic circulation (Fig. 2) (2). The net result is incomplete bioavailability due to first-pass metabolism (inactivation), and/or metabolic formation of a pharmacologically active species.

The physicochemical and biopharmaceutical properties of the drug can have a tremendous impact on its bioavailability and, hence, on its efficacy and toxicity profile. Thus, understanding these parameters is often tantamount to the selection and development of the optimum dosage form.

These properties of the drug are its:

- pH solubility profile and dissolution rate
- Partition coefficient between lipoidal barriers and aqueous physiologic media
- Stability and/or degradation rate in the physiologic fluids
- Susceptibility to metabolic inactivation
- Mechanism of transport through biologic membranes.

The aqueous solubility of a drug in the 2–8 pH range has a direct influence on its oral and parenteral formulations. A drug with poor solubility (i.e., less than 0.1 mg/ml) in acidic media may show poor and erratic oral bioavailability due to the dependency of absorption processes in GI fluids. Intravenous dosing requires that the drug be administered in a soluble form. The adjustment

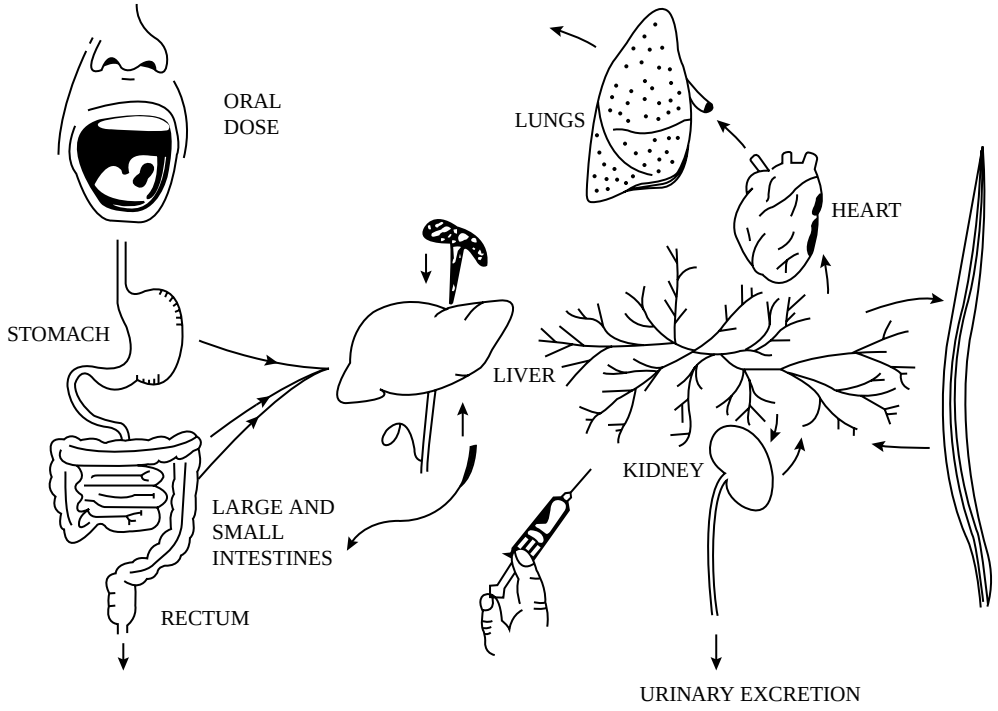

Fig. 1 Physiological factors associated with bioavailability. (From Ref. 1.)

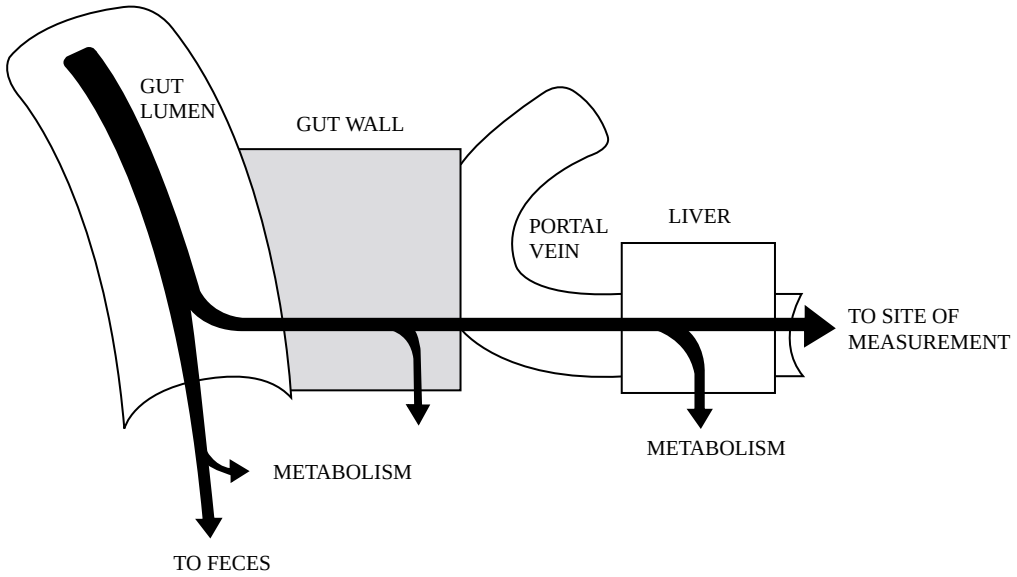

Fig. 2 A drug, given as a solid, encounters several barriers and sites of loss in its sequential movement during gastrointestinal absorption. Dissolution, a prerequisite to movement across the gut wall, is the first step. Incomplete dissolution or metabolism in the gut lumen or by enzymes in the gut wall is a cause of poor absorption. Removal of a drug as it passes through the liver further reduces absorption. (From Ref. 2.)

of pH, the addition of a cosolvent or a ligand for complexation, or the formation of an emulsion may permit solubilization, but each of these techniques has limitations. Rapid intravenous administration of a solubilized drug can result in rapid dilution in an environment in which the drug is insoluble, resulting in incomplete availability and a delayed response due to the formation of particulate matter within the vascular system.

Poor aqueous solubility is not always a limitation; in fact, it may be a desirable feature for a sustained effect after oral or parenteral administration. Oral sustained release may be achieved if the drug combines poor aqueous solubility with the ability to be adsorbed throughout the GI tract. Parenteral sustained release can be achieved after intramuscular administration of a suspension of a drug with low solubility under physiologic conditions or from a drug that precipitates from an aqueous vehicle or that forms a reservoir or depot from an oil-containing dosage form.

The lipid-aqueous partition coefficient of a drug molecule affects its absorption by passive diffusion. In general, octanol/pH 7.4 buffer partition coefficients in the 1–2 pH range are sufficient for absorption across lipoidal membranes. However, the absence of a strict relationship between the partition coefficient of a molecule and its ability to be absorbed is due to the complex nature of the absorption process. Absorption across membranes can be affected by several diverse factors that may include the ionic and/or polar characteristics of the drug and/or membrane as well as the site and capacity of carrier-mediated absorption or efflux systems.

Compounds that are intended for oral administration and can undergo rapid degradation at low pH may require protection from the acidic environment of the stomach. Protection can often be afforded by administering the drug in the form of an acid-insoluble chemical species or in a dosage form with an acid-resistant coating. The insoluble chemical species must remain insoluble and unavailable for solution degradation as it passes through the stomach and must dissolve upon reaching the chemically more stable environment of the intestine at a higher pH. To be effective, an acid-resistant coating must remain intact and protect its contents until it reaches the required pH to dissolve the coating and release the contents in the intestine where the drug may be more stable.

Metabolic inactivation of a compound following oral administration can occur in the GI lumen, the GI mucosa, or the liver. The site of metabolism and the susceptibility of the metabolic processes to saturation are factors that may influence oral bioavailability. Occasionally, some of these factors may be altered to optimize oral bioavailability. For example, segment specific metabolic sites within the GI tract may be avoided through the use of pH-dependent coating materials that rely on the local pH environment of the GI tract to release the drug. Absorption from the lower colon and rectum can reduce exposure to the portal circulation and the first-pass inactivation that can occur in the liver and, thus, provide the opportunity to improve systemic availability following oral administration. Enzyme systems may be saturated by the rapid release of the contents of the dosage form at a local site or by coadministration within the dosage form of a competitive inhibitor.

Once the physicochemical and biopharmaceutical properties of the drug are determined and the desired plasma concentration profile is defined, the pharmaceutical scientist can select and develop an efficacious dosage form by utilizing a formulation approach, a prodrug approach, a device approach, or an alternative administration route approach.

FORMULATION APPROACH

Use of formulation techniques can improve the bioavailability and/or minimize the toxicity and side effects of drugs. Factors to consider include those that impact on solubility and dissolution rates, chemical and enzymatic stability, and absorption capability.

Several parameters, including particle size, crystalline habit, and salt form, can affect the solubility and dissolution rates of the drug. The effect of particle size on the dissolution rate of relatively insoluble compounds becomes significant when the drug is administered as a suspension or solid dosage form and the material is well dispersed within the GI tract. However, caution must be exercised when compressing the material into a final dosage form because excessive force can result in particle agglomeration and an actual increase in the effective particle size.

Polymorphism is the ability of a chemical species to crystallize in more than one distinct crystal habit. The pharmaceutical applications of polymorphism have been reviewed by several authors (3–5). The differences in dissolution rate and solubility that polymorphs can produce may have a dramatic impact on bioavailability when dissolution is the rate-limiting step in the absorption process.

Tawashii (6) investigated the GI absorption of two polymorphs of aspirin, the stable and metastable forms, forms I and II, respectively. He found that the metastable

form produced a 70% higher total serum salicylate levels than the stable form I.

The selection of a salt form directly influences the physicochemical and biopharmaceutical properties of a compound. The impact of salt selection has been reviewed (7–9). Nelson (10) examined the dissolution of theophylline salts and commented on their impact on oral administration. The dissolution rates of the theophylline salts proceeded independently of the pH of the medium but was governed by the diffusion layer pH. The choline and isopropanolamine salts dissolved three to four times faster than the ethylenediamine salt and produced higher and prolonged blood levels.

For highly insoluble amine bases, such as ergotamine and certain antimalarials, the drug may precipitate in the small intestine as soon as the pH rises following stomach emptying. The authors' experience has been that committing the effort and expense required to develop a new, more soluble salt form of this type of drug may be futile, especially if the new salt is only two to three times more soluble than existing salts. Thus, the selection of the most appropriate salt form should be made early in the development process to optimize bioavailability.

The stability of a drug in the gut is influenced by both chemical and enzymatic factors. Protection from chemical degradation may be accomplished via coating techniques, and enzymatic protection ma be achieved with enzymatic inhibitors.

An enteric coating protects the drug during transit through the acidic medium of the stomach. Upon entering the higher pH environment of the duodenum, the coating is dissolved, and the drug becomes available for absorption. Such a coating also provides protection for the gut mucosa when the drug is capable of producing GI irritation. This method has been employed for a number of drugs, including potassium chloride, ammonium chloride, aspirin, diethylstilbestrol, erythromycin, and divalproex. Nishimura et al. (11) employed enteric coating of levodopa to improve its bioavailability. Levodopa is absorbed from the upper portion of the small intestine but undergoes rapid degradation in the intestinal mucosa by levodopa decarboxylase. The authors developed an enteric-coated dosage form with an effervescent core. The dosage form remains intact through the stomach, dissolves upon reaching the small intestine, and bursts open due to the effervescence of the incorporated sodium bicarbonate (Fig. 3). The rapid release in the duodenum results in concentrations of levodopa sufficient to saturate the enzyme at the absorption site.

The limitations of enteric-coated dosage forms include the possibility of duodenal irritation from caustic drugs and an increase in intersubject variability due to the presentation to the small intestine of a dosage form that needs to undergo disintegration and dissolution versus a disintegrated and partially dissolved drug substance.

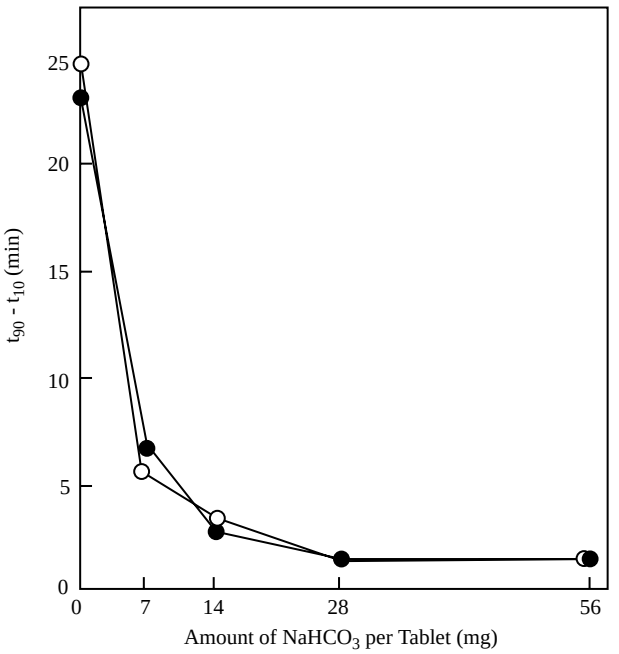

Fig. 3 Relationship between the dissolution parameter $t_{90\text{-}10}$ of effervescent enteric tablets of levodopa and the amount of sodium bicarbonate formulated in the tablet. The number of strokes was fixed at 5/min and the pH was 7.5. Key: (●) = uncoated tablet; (○) = enteric tablet. (From Ref. 11.)

Enzyme inhibitors compete with the active drug for the enzyme and, thereby, reduce the degradation of the drug and deliver it more efficiently to the systemic circulation. An example is the carbidopa–levodopa combination. Carbidopa competes for levodopa decarboxylase, thereby reducing the levodopa degradation and improving the low bioavailability of levodopa.

Alternatively, the enzyme in the gut can be utilized to control the release of the active drug in the gut. For example, sulfasalazine, which is employed in the treatment of ulcerative colitis, is a combination of sulfapyridine and 5-aminosalicylate chemically linked via an azo bond. It remains absorbed and intact throughout the GI tract until it reaches the large intestine, where bacterial azoreductase enzymes degrade the azo bond and release sulfapyridine and 5-aminosalicylate to act locally on the lesions.

Altering the availability for absorption permits tailoring of the concentration-time profile for a drug. In the case of synthetic contraceptive steroids and theophylline dosage

forms, the approach should be to slow the release rate so that undesirable spikes in the plasma levels are minimized. This effect can be accomplished with a sustained-release formulation. In formulating a drug in a sustained-release dosage form, the following must be taken into consideration: the effective drug plasma level, the rate of absorption of the compound, the rate of elimination of the compound, and the site(s) of absorption. Having established these parameters, calculating the required release rate from the dosage form is a relatively simple matter and formulation techniques are readily available to produce the desired release rate. Predicted plasma levels for a steroid drug administered in sustained and conventional dosage forms are shown in Fig. 4.

The mechanism of absorption must always be evaluated when a sustained-release dosage form is considered. A drug that is passively absorbed throughout the GI tracts is an ideal candidate for sustained release. Drugs such as riboflavin, folic acid, aminopenicillins, amino-β-lactams and nucleoside analogs, which have windows of absorption due to site-specific and/or active transport processes, may have incomplete bioavailability when formulated in oral, sustained-release dosage forms.

PRODRUG APPROACH

An alternative to the formulation approach is the prodrug approach. A prodrug is defined as a drug that is prepared by chemically modifying a pharmacologically active species to form a new chemical entity that undergoes transformation to the active species within the body. The modification alters the physicochemical and biopharmaceutical properties of the drug in some beneficial manner.

The ideal prodrug should have the following characteristics:

- Possess no pharmacologic activity
- Be eliminated more slowly than its rate of cleavage to the parent
- Be nontoxic
- Be inexpensive to prepare.

Prodrugs can be used to increase or decrease the aqueous solubility, mask bitterness, increase lipophilicity, improve absorption, decrease local side effects, and alter membrane permeability of the parent molecule. For example, chloramphenicol has an aqueous solubility of 2.5 mg/ml, but chloramphenicol sodium succinate, a prodrug, has an aqueous solubility of 100 mg/ml. Hydantoins also possess low aqueous solubilites that result in low and variable availability and precipitation following injection. In an effort to increase the aqueous solubility of phenytoin, Stella et al. (12, 13) prepared the ethyl and triethylamine esters of diphenylhydantoic acid. The esters improved aqueous solubility by adding an amine function to the molecule, and under physiologic conditions, the cyclization to phenytoin is irreversible, rapid, and complete.

The perception of taste requires that some minimum aqueous concentration be exceeded so that the taste can be detected (perceived). As a result, bitterness can be masked by reducing solubility. The technique has been applied to

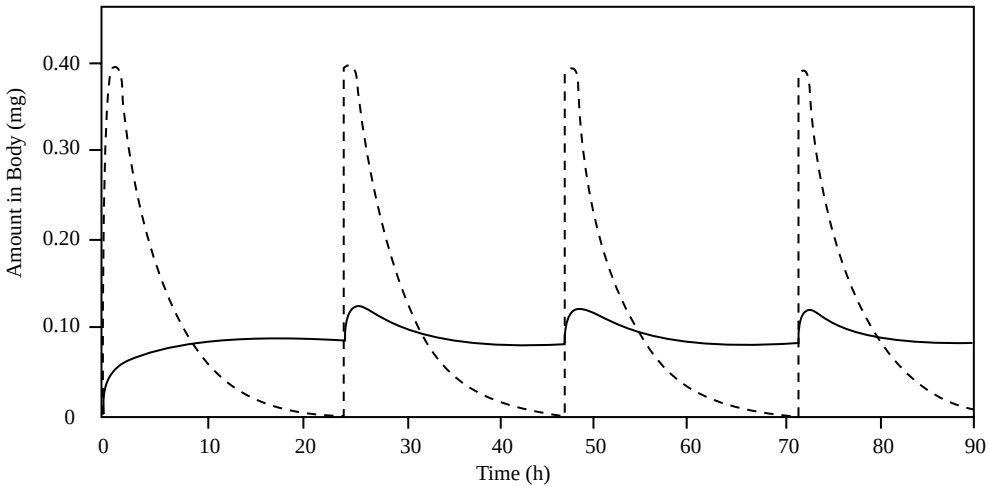

Fig. 4 Computer simulation of a plasma level-time profile of norethindrone from fast-releasing tablet (- - -) and sustained release tablet (—), from a dose of 0.5 mg/tablet and an elimination half-life of 3 h.

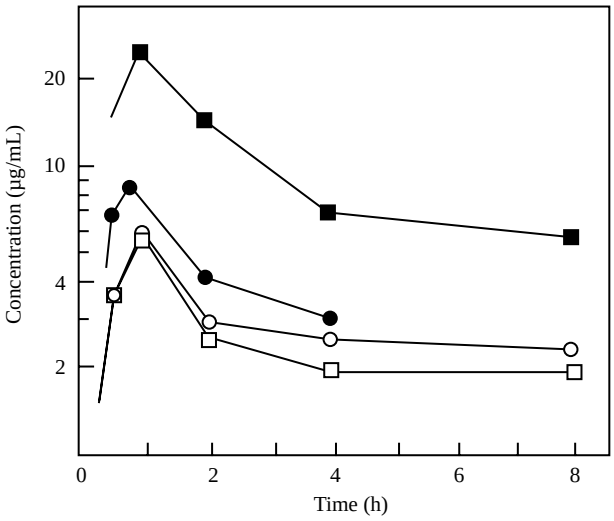

Fig. 5 Plasma acetaminophen concentration following the oral administration of acetaminophen and its ethyl vinyl ether prodrug. Dog 1 received 10 mg/kg doses of acetaminophen (○) and the prodrug (□). Dog 2 received 25 mg/kg doses of acetaminophen (●) and the prodrug (■). The 0.5-h prodrug and 8-h acetaminophen samples for dog 2 could not be obtained. (From Ref. 14.)

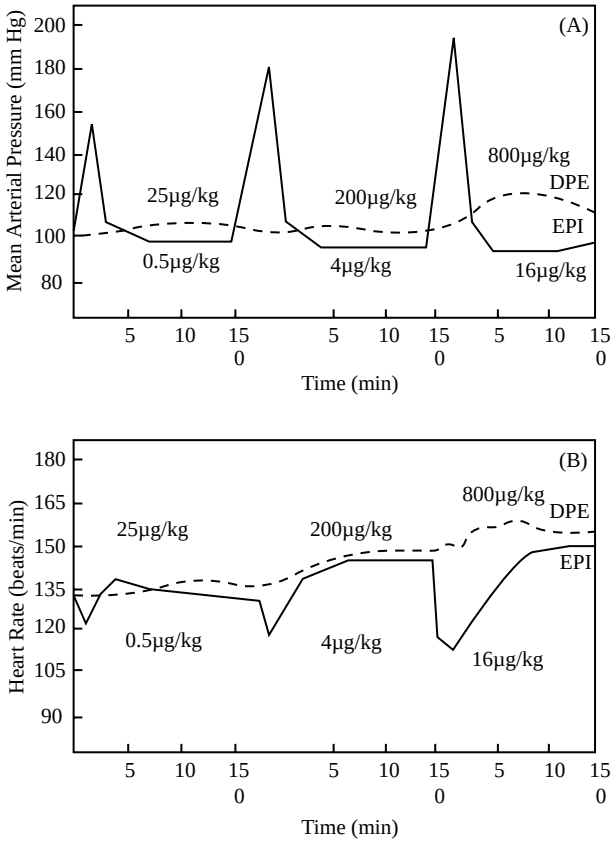

Fig. 6 (A) The effect of intravenous epinephrine (EPI) and its dipivaloyl prodrug (DPE) on blood pressure in dogs. (B) The effect of EPI and its DPE on heart rate in dogs.

acetaminophen by blocking the phenolic substituent with ethyl vinyl ether (14). Chemical hydrolysis to acetaminophen is rapid in the acidic conditions of the stomach. Plasma acetaminophen concentrations in dogs following oral administration of acetaminophen and the prodrug were found to be similar (Fig. 5).

Membrane permeability is governed in part by the lipophilicity of a compound. Highly polar compounds have low lipophilicities and, therefore, low membrane permeability. Epinephrine is a compound of this type. It is very effective in the treatment of glaucoma, but it produces a myriad of side effects. Ocular side effects include hyperemia, mydriasis, corneal edema, and allergic sensitivity. Systemic side effects, such as cardiac arrhythmias, elevated blood pressure, cerebral vascular accidents, dizziness, fear, and restlessness, are observed frequently. In an attempt to enhance the absorption and minimize the side effects of epinephrine, a prodrug, the dipivaloyl ester, was synthesized (15). It was found to be devoid of cardiac symptoms, with no effect on heart rate or blood pressure (Fig. 6) and was effective in lowering intraocular pressure (IOP) (Fig. 7).

On the other hand, highly lipophilic compounds, such as hormones, can be solubilized via the prodrug approach. For example, the rate of transdermal absorption of the highly lipophilic drug, testosterone, was enhanced over 50-fold by forming water-soluble, yet lipophilic, prodrug ester (16). The prodrug testosteronyl-4-dimethylaminobutyrate was found to penetrate human skin tissue, in vitro, 54 times faster than testosterone itself (Fig. 8). Furthermore, the prodrug was found to generate testosterone rapidly in biological fluids by enzymatic hydrolysis (Fig. 9).

Oral administration of aspirin can result in gastrointestinal bleeding. The bleeding has been attributed to local irritation due to the acidic nature of the carboxylic acid substituent. In an attempt to reduce the gastric irritation of aspirin, acylal prodrugs were synthesized (17, 18). In vitro, the prodrugs generated rapidly aspirin and in a pH-independent fashion. The conversion to aspirin was very sensitive to changes in dielectric constant: decreases caused a corresponding decrease in the reaction rate. This sensitivity is strongly indicative of an S_N1 mechanism. The authors postulated that GI irritation would be reduced due to blockage of both the charge and the acidic nature of the aspirin.

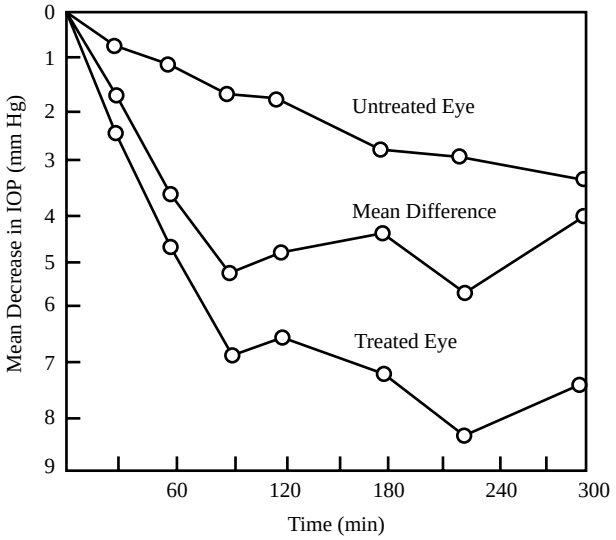

Fig. 7 The mean effect of one drop of 0.025% solution of the DPE of epinephrine on the intraocular pressure of nine glaucomatous individuals.

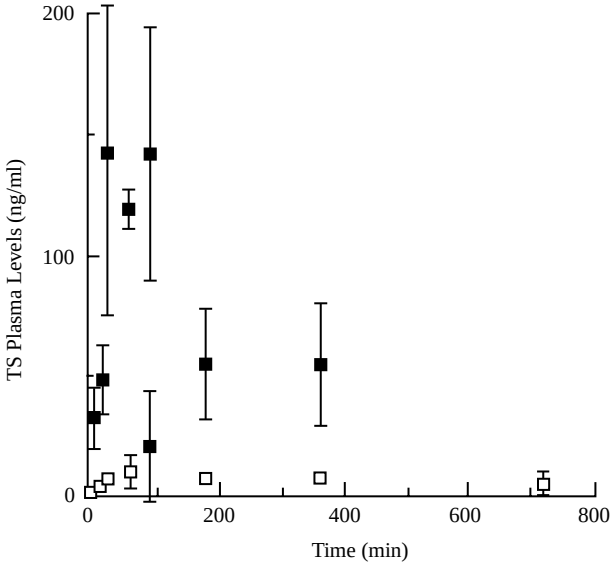

Fig. 9 Total plasma levels of TS (radioimmunoassay) after topical application of 1.25 μmol of TS (□) or TSBH (■) to the backs of HRS/J hairless mice $n = 6$. (From Ref. 16.)

DEVICE APPROACH

Controlling the release of medication at the site of action is often desirable, especially for compounds that are absorbed rapidly through mucous membranes or are removed rapidly from the site of action. The approach normally reduces the systemic side effects of the agent. The application of this approach can be illustrated with the Progestasert and Pilocarpine Ocusert dosage forms.

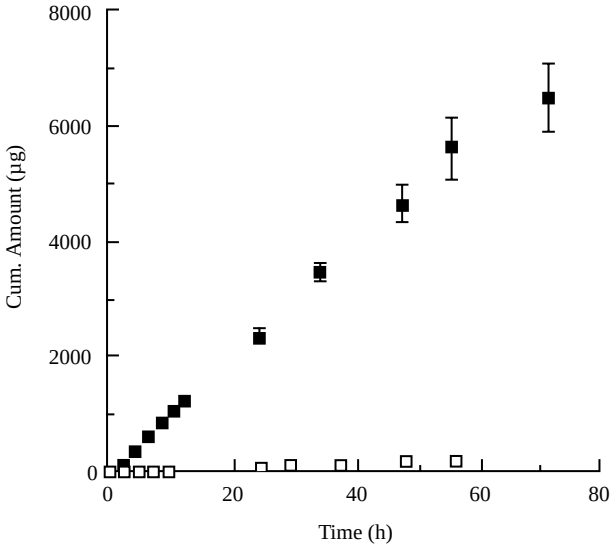

Fig. 8 Cumulative amounts of TS (□) and TSBH (■) crossing isolated human skin tissue in Franz cells ($n = 6$). TS was applied as a 10% suspension. TSBH was applied as a 10% solution. In each case, the vehicle was pH 7.4 phosphate buffer (0.2 *M*). (From Ref. 16.)

Diffusion-controlled devices may be designed for continuous release and usually use either a matrix or reservoir construction. In matrix systems, the drug is dispersed randomly throughout a polymer, whereas reservoir devices surround the drug with an intact rate-controlling membrane. Regardless of the method of construction, the system must be safe and biocompatible for biological application.

The Progestasert intrauterine device (IUD) is a contraceptive IUD marketed in the United States. It is a white, T-shaped unit constructed of ethylene-vinyl acetate copolymer containing titanium dioxide. It releases progesterone at a rate of 65 μg/day for 1 year, controlled by an outer coat of ethylene-vinyl acetate copolymer. Zaffaroni pointed out several advantages to the uterine progesterone system (19). It permits target-specific delivery of a fertility-control agent for up to 1 year by utilizing a single natural hormone at the lowest effective level of release of hormonal activity. The 1-year duration gives improved patient compliance while eliminating the pulsing seen with repetitive oral or injectable regimens. The efficacy of the Progestasert was investigated by Aznar and Giner (20). Their results indicated that the systems are highly efficacious in avoiding accidental pregnancy and result in decreased menstrual blood loss.

The Pilocarpine Ocusert is a contact lens-shaped device that is inserted into the lower cul-de-sac of the eye. It provides continuous release of pilocarpine at a rate of 10 or 20 μg/h, over a 1-week period, for the treatment of open-angle glaucoma. The system is capable of producing significant lowering of ocular pressure and constriction of the pupillary diameter (21). Its use greatly enhances patient compliance and the convenience of the therapeutic regimen while reducing local and systemic side effects.

Armaly and Rao examined the clinical effects of the Pilocarpine Ocusert systems with different release rates (22). The systems exhibited a dose-response relationship such that increases in the release rate above 50 μg/h resulted in increased ocular hypotensive effects with no appreciable change in ocular pressure. The reduction in pressure observed at the 50 μg/h rate was comparable with the changes seen after the administration of 4–8% of pilocarpine solutions.

ALTERNATIVE ADMINISTRATION ROUTES

The administration of drugs by alternative routes avoids absorption and metabolic barriers that may be present in the GI tract. The routes can also provide systematic availability when oral administration is contraindicated due to a physiologic condition, or the route may provide for a concentration-time profile that approaches intravenous dosing profiles. The ophthalmic, nasal, pulmonary, buccal, transdermal, and rectal routes provide one or more of these advantages.

The ophthalmic route has been used traditionally for topical application for local effects. However, with the increasing number of peptide drugs being developed, the ophthalmic route has been considered for systemic drug delivery (23). After topical administration in the eye, peptides can be absorbed from the mucosa during tear turnover as well as via the blood vessels of the conjunctiva. The route suffers from the hesitancy of practitioners to place a drug into the eye for any reason other than to produce ophthalmic effects. Another drawback is the sensitivity of the eye to irritation by foreign substances.

Nasal administration produces rapid blood levels and rapid responses that approach those obtained from intravenous dosing. In addition, the absorbed drug does not pass through the liver before reaching the systemic circulation, and, thus, first-pass metabolism is avoided. In recent years, the nasal route has received a great deal of attention as a convenient and reliable route for the systemic administration of drugs, especially those that are ineffective orally and must be given by injection. Recently, butorphanol tartrate was introduced commercially in a nasal spray dosage form (Stadol NS®) for the relief of pain, such as migraine headache (24). It would appear that the nasal route could be considered for drugs that meet the following criteria: are ineffective orally; are used chronically; are used in small doses; and are desirable to have rapid entry to the general circulation.

Published work carried out in many laboratories has shown that, with the notable exception of the peptides, drugs with a wide variety of chemical structures are well absorbed through the nasal membranes of animals and man. It is believed by many authors that in vivo nasal absorption of compounds with molecular weights less than 300 daltons is not significantly influenced by the physicochemical properties of the drug molecule (25). Factors, such as the size of the molecules and, in the case of peptides, their ability to hydrogen bond with the component(s) of the membrane, are more important than their lipopohilicity and their ionization state. For example, the in vivo rate of absorption of the very lipophilic drug progesterone is similar to that observed for sodium benzoate, and the in vivo rate of absorption of benzoic acid is independent of the pH of the medium (26).

Although many drugs are absorbed rapidly and quantitatively following nasal administration, peptides have generally shown low bioavailabilities. Hussain et al. examined the nasal bioavailability of leucine enkephalin (27). The low bioavailability of this pentapeptide was attributed to hydrolysis in the nasal cavity, with dipeptides causing significant inhibition of the hydrolysis. They concluded that polar compounds, such as peptides, can cross the nasal mucosa, and that administration of low concentrations results in extensive hydrolysis in the nasal mucosa and that hydrolysis of leucine enkephalin can be reduced by concomitant administration of peptidase labile peptides.

If the presence of a pharmacologic activity for a peptide is the only criterion for its use in therapy, then nasal administration may be employed, even though bioavailability is not 100%. However, when bioavailability, as determined by plasma level profiles, is considered, the nasal route for peptide administration is not optimal unless enhancers are employed. Enhancers may cause irritation and reduced membrane integrity. Other drawbacks of nasal delivery include the small volume permitted (i.e., 0.2 ml or less), the need for highly potent drugs with low doses, the potential for irritation, and the unknown consequences of long-term nasal administration of drugs, adjuvants, and other formulation components.

The buccal and sublingual routes of administration permit rapid delivery to the systematic circulation. Absorption from the buccal and sublingual vasculature and lymphatics bypasses hepatic circulation and, thereby, reduces first-pass metabolism. The driving force of absorption is the high thermodynamic activity of the compounds. Organic nitrates and testosterone have been administered by these routes to produce rapid plasma concentrations and to minimize hepatic metabolism.

The sublingual administration of methyltestosterone was examined by Alkalay et al. (28) The sublingual tablet produced a 50% higher relative bioavailability when compared with the oral tablet or oral solution. The increased bioavailability was attributed to the avoidance of first-pass hepatic metabolism due to absorption from the sublingual vasculature and lymphatics.

The limitations of the buccal and sublingual routes include the requirement for successful candidates to possess high thermodynamic activities, the restrictive size of the buccal pouch and sublingual area, and the concern over the palatability and local irritation by the compound.

Transdermal administration can avoid first-pass metabolism as well as provide a large surface area for continuous–controlled administration of drugs with short biological half-lives and narrow therapeutical indices. The route has been used for nitroglycerin ointments, and transdermal therapeutical systems (patches) have been developed for scopolamine, nitroglycerin, clonidine, estradiol, and nicotine.

Scopolamine can cause side effects of dry mouth, drowsiness, tachycardia, central nervous system (CNS) disturbances, and amnesia if plasma concentrations exceed the levels required to alleviate motion sickness (Fig. 10). The application of scopolamine to the posterior auricular areas (the most permeable anatomical site) via a microporous patch permits constant delivery of 0.5 mg over 3 days to prevent motion sickness and avoid side effects.

The transdermal route suffers from the inability of the skin to deliver large doses, the relatively slow plasma increase when compared with other routes, and the potential for irritation. However, several products utilizing this route of administration are currently on the market. Absorption can be enhanced with molecules that maintain an appropriate hydrophilic–lipophilic balance for efficient passage through the barrier of the stratum corneum (16).

Rectal administration of systemic effect has traditionally been limited to clinical situations where oral intake is restricted due to a physiologic condition (e.g., vomiting) or to compounds that are irritating to the gastric mucosa. The route has been utilized for aspirin, acetaminophen, aminophylline, promethazine, perchlorpromazine, chlorpromazine, and indomethacin. The rectal administration of drugs is limited by increased interpatient variability and patient acceptability.

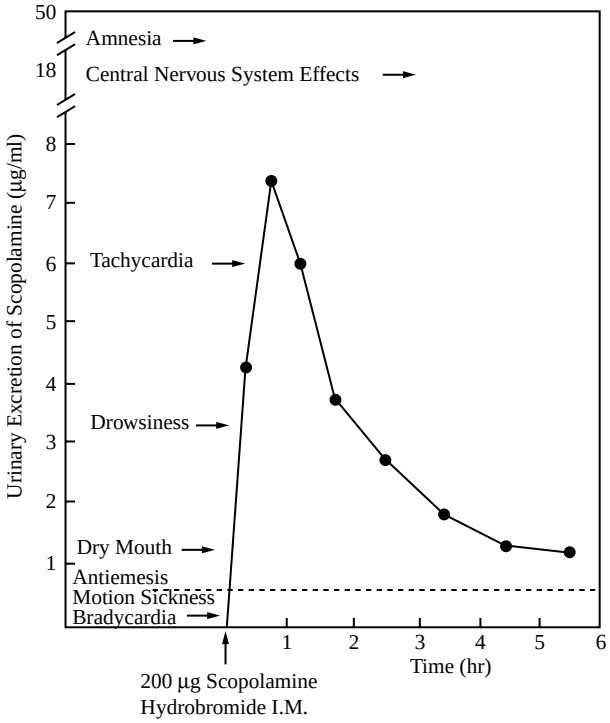

Fig. 10 Relationship between urinary excretion rate of scopolamine and its pharmacological effects; 10% of a parental dose of scopolamine is excreted in the urine unchanged.

This section has reviewed some of the dosage form design methods available to the pharmaceutical scientist that have been shown to improve the therapeutic efficacy of certain drugs. The key to optimal dosage form design lies in the prerequisite understanding of the physicochemical and biopharmaceutical properties of the drug and the available routes of administration. Once the compound has been characterized and the problem has been defined, the technology is available to optimize bioavailability.

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